

4/PRTS

INHIBITION OF RENAL UPTAKE OF MOLECULES THAT ARE  
POTENTIALLY DAMAGING FOR THE KIDNEY

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The present invention relates to the inhibition  
5 of renal uptake of molecules that are potentially  
damaging for the kidney.

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Radionuclide labeled peptides and also  
monoclonal antibodies or their fragments and other  
compounds like certain antibiotics undergo undesired  
10 renal uptake and cellular retention leading to a high  
kidney dose, or concentration. In the case of diagnosis  
or therapy with radiolabeled proteinaceous compounds,  
like peptides and monoclonal fragments, the uptake of  
these compounds by the kidneys leads to a reduction in  
15 the detection sensitivity of perirenal tumors or an  
increase in kidney radiotoxicity.

In certain other situations a general overload  
of proteins in the kidney can occur, such as in the case  
of amino acid metabolism diseases, induced catabolism or  
20 prolonged physical exercise, e.g. long-distance running.

Increased amounts of protein or raised doses of  
radiation or toxic substances in the kidneys may  
eventually lead to kidney damage.

International patent application No.

25 WO91/04755, filed September 24, 1990, teaches methods to  
reduce non-target kidney retention of immunoconjugates,  
metabolites thereof, including other substances, such as  
peptides, by coadministration of a non-target moiety,  
such as lysine, or other amino acids having a free amino  
30 group. The application discloses only experimental  
results with mice showing that higher doses of lysine as  
a non-target reduction moiety improved results, i.e. the  
percentage of the injected immunoconjugate dose detected  
in the kidney is decreased. However, no information is  
35 provided concerning the possible toxicity of the method,  
and no data in humans were supplied. It is a known fact  
that there are differences in the physiology, including  
the renal physiology between mice and humans.

Additionally, it is known that infusion of amino acid solutions can induce side effects, including hyperkalemia (e.g. Ponce SP, et al. Medicine 64: 357-370, 1985, and Sartori S, et al. Recenti Progressi in Medicina 82(6): 275-277, 1991). This has been reported in particular for arginine (e.g. Massara F, et al. Diabete et Metabolisme 5(4):297-300, 1979), but it is also known in general medical practice for lysine, among others (Speck SP. in: Rakel RE, ed. Saunders Manual of Medical Practice; W.B. Saunders Company, Philadelphia, 2000, pp 885-888).

It is furthermore a known practice to use in patients an infusion of commercially available cocktails of various amino acids to lower the uptake of radiolabeled pharmaceuticals such as [ $^{111}\text{In}$ -DTPA-D-Phe<sup>1</sup>]octreotide in the kidney (Hammond et al. in Br. J. Cancer 67, 1437-1439 (1993), Barone R, et al., J. Nucl. Med, 41: 94P (2000)). Such cocktails usually comprise a total amount of about 100 grams or more of various amino acids. In order to keep the osmolarity of such mixed amino acid solutions tolerable for human infusion, the total volume will be in the range of 2 liters.

This type of treatment has the observed disadvantageous side-effect that patients may suffer from severe vomiting, presumably caused by toxicity of the high total amount of amino acids administered. Additionally, the infusion of any volume of 2 liters within 4 hours, especially when it is hyperosmolar, can be dangerous to patients with impaired cardiac or renal function.

For the purpose of the invention, i.e. inhibiting renal uptake, it is necessary to reach a particular serum level of amino acids within a relatively short time, because excretion of the bulk of radiopharmaceuticals occurs within the first 4 to 6 hours after administration. During this time the radiopharmaceuticals may be taken up by the kidneys. It is thus not possible to avoid the side-effect of vomiting

by administering the amino acid cocktail over a longer period of time.

Furthermore, it has been described by De Jong et al. in J. Nucl. Med 37(8): 1388-1392 (1996) that uptake in the rat kidneys of the [<sup>111</sup>In-DTPA-D-Phe<sup>1</sup>]octreotide can be inhibited by 50% by intravenous administration of the amino acid L-lysine alone (400 mg/kg). In a further article by Bernard et al. in J. Nucl. Med. 38: 1929-1933 (1997) it was demonstrated that also D-lysine is capable of reducing the rat renal uptake of [<sup>111</sup>In-DTPA-D-Phe<sup>1</sup>]octreotide and <sup>90</sup>Y-DOTA,Tyr<sup>3</sup>-octreotide.

However, treatment with lysine has also various disadvantages. It was for example found in humans that L-lysine in an effective total dose of 75 g (see examples for details) may lead to severe hyperkalemia which may result in acute and life-threatening cardiotoxicity in 50% of the patients.

In WO96/29087 it is also suggested to reduce kidney uptake of antibody fragment conjugates by administration of lysine or poly-lysine. It is taught in said application that toxicity of lysine can be avoided by using D-lysine because it does not occur naturally in humans or animals and is believed to be metabolically inert, thereby reducing the risk of toxic side-effects associated with the use of L-lysine. The prescribed dosage of monomeric lysine in this application is 1-200 g. The examples do not give results of treatments with humans with lysine alone. The only experiments in humans are performed with the commercially available amino acid solution Periamin X<sup>TM</sup>. According to the invention it is now shown that even 75 g of lysine is too high a dose. This already indicates that WO96/29087 may mention, but does not really enable the use of lysine in humans.

From the prior art it thus follows that reduction of renal uptake of unwanted proteinaceous materials can be achieved by either the use of amino acid cocktails that are commonly used as parenteral food

supplements or with lysine alone. Either method has however the disadvantage that it may lead to toxic effects in humans.

It is therefore the object of the invention to  
5 provide a new improved way of inhibiting the renal tubular uptake of various types of proteinaceous molecules, such as proteins, peptides and antibodies.  
10 *03* This is achieved by the invention by the use of the combination of:

- 04*
- 10 - a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and
  - 15 - a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof,
- for the preparation of a composition for inhibiting renal uptake of proteins or peptides, that are used for  
20 therapeutical or diagnostic purposes.

Preferred positively charged compounds are amino acids, e.g. arginine, ornithine or citrulline. The preferred positively charged amino acid for use together with lysine is arginine.

*05*  
25 It was found that 50% inhibition in renal uptake of [<sup>111</sup>In-DTPA-D-Phe<sup>1</sup>]octreotide in rats could be achieved by D-Lysine or L-lysine at 400 mg/kg. L-arginine alone gave a reduction of 20-30% at an equimolar dose. In human studies 15, 21 and 40% reduction of kidney uptake  
30 of [<sup>111</sup>In-DTPA-D-Phe<sup>1</sup>]octreotide was reached using a dose of 25, 50 and 75 g L-lysine, respectively. The doses of 25 and 50 g L-lysine were well tolerated without any toxicity noted, but the 75 g L-lysine dose was associated with severe hyperkalemia in 50% of the patients.  
35 Hyperkalemia may result in acute and life-threatening cardiotoxicity.

The combination of L-lysine and L-arginine, however, shows a synergistic effect and is more effective

than both compounds alone at equimolar concentrations in reducing renal uptake of radiolabeled peptides. Using the combination, lower doses of the two amino acids can therefore effectively inhibit the (radio)pharmaceutical renal uptake and simultaneously prevent hyperkalemia and cardiotoxicity. The normal serum potassium values lie between 3.5 and 5.3 mmol/L. Values between 5.3 and 6.0 mmol/L are a grey area. Values above 6.0 mmol/L are not acceptable, and cardiotoxicity may occur.

An additional advantage of the use of the two compounds of the invention is that the total infusion volume can be kept to 1 liter, which is safer than 2 liter in patients with compromised renal or cardiac function.

The treatment of the invention was found to have a lower impact on the increase in potassium level in serum than a treatment with 75 g lysine in 1500 mL. Whereas in the latter case 3 out of 6 patients had a maximum potassium level above the critical value of 6.0 mmol/L, the treatment of the invention resulted in only one out of eleven patients having a maximum potassium value of 6.0 mmol/L.

It is assumed that a possible mechanism of action of the invention is based on a blockade of megalin, a type I membrane glycoprotein of 4630 amino acids, 600 kDa, and having a pI of 4.6 that mediates renal tubular reabsorption. Megalin's mechanism of action is based on endocytosis through coated pit vesicles. Megalin transports positively charged molecules and is found on the brush border of proximal tubular cells, thyroid follicular cells, parathyroid cells, in the mammary gland, placenta, yolk sac and on lung type II pneumocytes.

The inhibition of renal uptake of proteins and peptides can be effected during therapy and diagnosis to protect the kidneys from detrimental side-effects of the therapeutic or diagnostic materials. In addition, when tissues surrounding the kidneys are subjected to

localization with radiolabeled proteins or peptides, renal uptake of these radioactive materials may interfere with the scintigraphic visualization due to radiation from the kidneys that obscures the radiation from these surrounding tissues. Inhibition of accumulation of radioactivity in the kidneys is then also desirable.

It was also found according to the invention that after treatment with the combination of L-lysine plus L-arginine during radiotherapy with [ $^{177}\text{Lu}$ -DOTA,Tyr<sup>3</sup>] octreotate none of the 11 patients treated suffered from vomiting. In contrast, with the treatment with a cocktail of several amino acids (see examples for the details) 42% of the patients vomited who received radiotherapy with  $^{90}\text{Y}$ -DOTA,Tyr<sup>3</sup>-octreotide. In 45% of these patients vomiting was very severe, i.e. 5 to 30 times. In another experiment it was found that in only 8% of treatments with the L-lysine and L-arginine combination vomiting occurred, mainly observed in one single patient, and this were probably not related to this combination.

The invention is suitable for inhibiting the renal uptake of all sorts of proteinaceous materials, such as proteins, peptides and monoclonal antibodies or their fragments. Renal uptake is to be avoided in case the proteinaceous materials are inherently toxic for the kidneys, and when they are coupled to a toxin, a radionuclide, a cytostatic agent or other potentially detrimental product. Renal uptake of nephrotoxic antibiotics or cytostatic agents per se is also to be prevented. In some cases the uptake by the kidneys of other, non-detrimental proteins can also be a problem. Protein is metabolized by the liver and excreted by the kidneys into the urine. A high protein load causes damage to these organs. In addition, diseases related to amino acid metabolism could lead to a protein overload in the kidneys.

Specific examples of diagnosis and therapies in which the composition of the invention could be used to inhibit or prevent renal uptake of the diagnostic or

therapeutic agent are the use of radiolabelled peptides, including but not limited to octreotide and other somatostatin analogs, labelled with  $^{111}\text{In}$ ,  $^{90}\text{Y}$ ,  $^{177}\text{Lu}$ ,  $^{131}\text{I}$  or any other suitable radionuclide. Further examples are  
5 the diagnostic and therapeutic application of monoclonal antibodies or their fragments, nephrotoxic drugs such as antibiotics and cytostatic drugs.

In all these and other situations, the inhibition of the uptake of proteins or pharmaceuticals  
10 by the kidneys according to the invention can be beneficial.

The invention further relates to therapeutical compositions for inhibiting the renal uptake of proteins or peptides, that are used for therapeutical or  
15 diagnostic purposes, which composition comprises one or more suitable excipients, carriers or diluents and a combination of

- a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino  
20 group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and

- a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or  
25 carboxyl derivatives thereof.

Preferred positively charged compounds are amino acids, e.g. arginine, ornithine or citrulline. The preferred positively charged amino acid for use together with lysine is arginine.

30 In a preferred embodiment of the composition it comprises lysine and arginine. The amount of lysine in the composition is between 10 and 45 grams, preferably between 15 and 35 grams, more preferably between 20 and 30 grams, most preferably about 25 grams. The amount of  
35 arginine is between 15 and 45 grams, preferably between 15 and 35 grams, more preferably between 20 and 30 grams, most preferably about 25 grams. Such amounts are preferred for administration in 1 L over 4 hours.

Preferably the total amount of the two compounds does not exceed 100 grams, is preferably less than 75 grams and is more preferably not more than 50 grams. The amounts given are intended for adults. For children the usual  
5 modifications can be made.

In this application the term "first compound" should be understood to refer to one or more members selected from the group consisting of lysine, poly-lysine, pharmaceutically acceptable salts or carboxyl  
10 derivatives thereof, as well as amino acids or other proteinaceous moieties having a free amino group with a pKa substantially similar or equal to that of lysine. The "second compound" is to be understood to refer to one or more positively charged compounds, preferably selected  
15 from among positively charged amino acids, more preferably selected from among arginine, ornithine and citrulline or poly-amino acids or pharmaceutically acceptable salts or carboxyl derivatives of the positively charged amino acids. The preferred combination  
20 is such that the first compound is lysine, which may be either D-lysine, L-lysine or poly-lysine. The second compound is preferably arginine, which may be either D-arginine, L-arginine or poly-arginine.

The therapeutical composition of the present  
25 invention can be in an oral or parenteral dosage form. Parenteral dosage forms include intravenous, intraarterial, intraperitoneal, intramuscular and subcutaneous dosage forms, preferably intravenous dosage forms. Administration may be via a single or via multiple  
30 boluses, or by continuous or discontinuous infusion and is preferably by continuous infusion over 4 hours, starting about 30 minutes prior to administration of the radiopharmaceutical.

The combination of compounds of the present  
35 invention may be administered in any pharmaceutically acceptable solution. A solution is said to be pharmaceutically acceptable if its administration can be tolerated by a recipient patient. Sterile phosphate-



buffered saline is one example of a pharmaceutically acceptable carrier, as is Ringer lactate, Hartman's solution or a mixture of glucose and saline. Other suitable carriers are well-known to those skilled in the art.

The present invention will be further illustrated in the examples that follow and that are not intended to limit the scope of the invention.

In the examples reference is made to the following figures:

**Figure 1** shows the ratio between [ $^{111}\text{In}$ -DTPA-D-Phe<sup>1</sup>]octreotide uptake in various organs in the presence or absence of 1 L lysine/arginine infusion (25/25 g; administered over 4 hours). Filled dots represent non-targeted accumulation of the radiopharmaceutical. Open squares represent the targeted accumulation of the radiopharmaceutical.

**Figure 2** shows the ratio between [ $^{177}\text{Lu}$ -DOTA, Tyr<sup>3</sup>]octreotate uptake in various organs in the presence or absence of 1 L lysine/arginine infusion (25/25 g; administered over 4 hours). Filled dots represent non-targeted accumulation of the radiopharmaceutical. Open squares represent the targeted accumulation of the radiopharmaceutical.

**Figure 3** shows the ratio between [ $^{111}\text{In}$ -DTPA-D-Phe<sup>1</sup>]octreotide uptake in various organs in the presence or absence of 1 L glucose/saline solution, administered over 4 hours. Filled dots represent non-targeted accumulation of the radiopharmaceutical. Open squares represent the targeted accumulation of the radiopharmaceutical.

**Figure 4** shows between [ $^{111}\text{In}$ -DTPA-D-Phe<sup>1</sup>]octreotide uptake in the left kidney after a 0.5 + 3.5 hour infusion of various amino acid compositions.

EXAMPLES**MATERIALS*****Composition of infusion fluids***

5

**A. Lys/Arg**

Combination of L-lysine and L-arginine (total 1000 mL)

- L-arginine HCl 10%      250 mL (=25 grams of L-arginine)
  - L-lysine HCl 5%      500 mL (=25 grams of L-lysine)
  - 10 • HCl 25% is added to achieve pH 7.4
  - NaCl 0.9% is added to achieve a total volume of 1000 mL
- The osmolarity of this combination is ca. 400 mosmol/L  
The total quantity of amino acids is 50 grams.

15 **B. Cocktail of various amino acids (total 2030 mL)**

- Aminosteril N-Hepa 8%      1500 mL
- Ringer lactate      500 mL
- Magnesium sulfate (7-water) 10%      30 mL

The osmolarity of this combination is ca. 700 mosmol/L

- 20 The total quantity of amino acids is 124.5 grams.

Aminosteril N-Hepa 8% is a commercially available solution containing a mixture of amino acids (Fresenius AG, Gluckensteinweg 5, D-6380 Bad Homburg v.d. H., Germany). The composition is given herein below.

Ringer lactate is a mineral solution containing NaCl 0.6%,  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  0.04%, Na-lactate 0.322% (Baxter B.V., Energielaan 3, NL-5405 AD Uden, The Netherlands)

30

Composition of Aminosteril N Hepa 8% infusion fluid

SUBSTANCE	QUANTITY (g/L)	Total in 1500 mL	
L-isoleucine	10,40	15,600	
L-leucine	13,09	19,635	
L-lysinemonoacetate (= 6,88 g L-lysine)	9,71 (6.88)	14,565	(10.32)
L-methionine	1,10	1,650	
Acetylcysteine (= 0,52 g L-cysteine)	0,70 (0.52)	1,050	(0.78)

L-fenylalanine	0,88	1,320
L-treonine	4,40	6,600
L-tryptophane	0,70	1,050
L-valine	10,08	15,120
L-arginine	10,72	16,080
L-histidine	2,80	4,200
Aminoacetic acid (glycine)	5,82	8,730
L-alanine	4,64	6,960
L-proline	5,73	8,595
L-serine	2,24	3,360
Acetic acid	4,42	
<b>Total amino acids</b>	<b>83,01 g/L</b>	<b>124,52 grams</b>
<b>Total nitrogen</b>	<b>12,90 g/L</b>	
<b>Osmolarity</b>	<b>770 mosm/L</b>	<b>770 mosm/L</b>

### C. L-Lysine (total 500 mL) per unit

- 5 • L-lysine HCl 5%                      500 mL (=25 grams of L-lysine)
- HCl 25% is added to achieve pH 7.4

The osmolarity of this solution is ca. 400 mosmol/L

For 50 grams of L-lysine 2 units (total 1000 mL) are  
 10 used; for 75 grams of L-lysine 3 units (1500 mL).  
 Saline (NaCl 0.9%) or a mixture of glucose and saline  
 (NaCl 0.45% + glucose 2.5%), can be added to increase the  
 infusion volume.

15 All these infusion fluids are given over a period of 4  
 hours, with a maximum of 2.03 L per 4 hours. The rate of  
 infusion can be constant over 4 hours, but initial high  
 rates of infusion followed by lower rates of infusion are  
 employed also. These infusion fluids can be given for  
 20 periods up to 12 hours, with maximal average infusion  
 rates of 2.03 L per 4 hours.

### EXAMPLE 1

Effect of intravenous Lysine/Arginine infusion on tissue  
 25 uptake

A 1000 mL infusion containing 25 g L-lysine and  
 25 g L-arginine (**Lys/Arg**; see MATERIALS, paragraph A. for

exact formulation) was administered intravenously to patients during 4 hours, starting 30 minutes prior to administration of the radioligand. One radioligand was [ $^{111}\text{In}$ -DTPA-D-Phe<sup>1</sup>]octreotide ( $^{111}\text{In}$ -pentetreotide, 5 OctreoScan®, Mallinckrodt Medical, Petten, The Netherlands) in a diagnostic amount of 220 MBq (9 patients). Each patient was also investigated on a separate occasion with 220 MBq  $^{111}\text{In}$ -pentetreotide, but without any infusion. The other radioligand was [ $^{177}\text{Lu}$ -DOTA,Tyr<sup>3</sup>]octreotate in a therapeutic amount of 1850 MBq 10 (5 patients). Each patient was also investigated on a separate occasion with 1850 MBq [ $^{177}\text{Lu}$ -DOTA,Tyr<sup>3</sup>]-octreotate, but without any infusion. The control experiment (5 patients) consisted of infusion of 1000 mL 15 neutral infusion fluid without the amino acids (NaCl 0.45% plus Glucose 2.5%) over 4 hours, starting 30 min. prior to the injection of 220 MBq  $^{111}\text{In}$ -pentetreotide.

24 Hours post infusion the uptake of the radioligand in the kidneys, spleen and liver was measured 20 using planar scintigraphy and dosimetry, and for each patient the ratio between uptake in these organs during infusion with **Lys/Arg** and without **Lys/Arg** was calculated (Figures 1, 2 and 3).

In the 9 patients who received a diagnostic 25 dose of 220 MBq of  $^{111}\text{In}$ -pentetreotide, during **Lys/Arg** infusion the mean uptake of the radioligand in the kidneys was reduced to 68% (left) and 52% (right) of their own control without **Lys/Arg** (Figure 1).

In the 5 patients who received a therapeutic 30 dose of 1850 MBq [ $^{177}\text{Lu}$ -DOTA,Tyr<sup>3</sup>]octreotate, during **Lys/Arg** infusion the mean uptake of the radioligand in the kidneys was reduced to 63% (left) and 61% (right) of their own control without **Lys/Arg** (Figure 2).

The control experiment showed no significant 35 differences in renal uptake of  $^{111}\text{In}$ -pentetreotide whether 1000 mL of (neutral) infusion fluid was administered or not, thus ruling out the infusion volume itself as a contributing factor to reduce renal uptake of  $^{111}\text{In}$ -

pentetreotide (Figure 3).

From these combined results it follows that there is a 40% decrease of  $^{111}\text{In}$ -pentetreotide or [ $^{177}\text{Lu}$ -DOTA,Tyr<sup>3</sup>]octreotate uptake in the kidneys during **Lys/Arg** infusion as compared to the control.

## EXAMPLE 2

### Effect of Lys/Arg infusion on serum potassium levels

In an experiment of the invention 11 patients received an infusion over 4 hours of a solution containing 25 g L-lysine and 25 g L-arginine in 1000 mL (**Lys/Arg**; see MATERIALS, paragraph A. for exact formulation). The potassium level of these patients was measured in serum at t=0 hours and after 0.5, 1, 2, 4 and 5 hours. The results are shown in table 1 and figure 4.

Table 1

Potassium level in serum during infusion of 1000 mL Lys/Arg over 4 hours, starting 30 min. prior to the administration of  $^{111}\text{In}$ -pentetreotide in a diagnostic amount of 220 MBq.

patient no.	0	0.5	1	2	4	5	max. difference
1	4.6	4.6	4.9	5.4	5.5	5.4	0.9
2	4.2	4.1	4.6		4.8		0.7
3	4.3	4.5	4.7	4.9	5.4	4.8	1.1
4	4.5	4.7	5.3	6.0	5.7		1.5
5	4.5	4.5		5.0	5.3		0.8
6	4.1	4.2		5.1	5.2	5.3	1.1
7	4.4	4.1		4.5	5.0		0.6
8	3.7	3.3		3.9	4.5	4.4	0.8
9	3.0	3.0		3.6	4.0		1
10	4.3	4.3		4.8	5.5		1.2

11	4.5	n.d.	4.4	4.9	4.8		0.4
Average	4.2	4.1	4.8	4.8	5.1		0.9

As a control 6 patients received 75 g L-lysine in 1500 mL during 4 hours (see MATERIALS, paragraph C. for exact formulation). Their maximum serum potassium levels are given in Table 2.

Table 2

Maximum potassium level in serum during infusion of 75 g L-lysine in 1500 mL over 4 hours, starting 30 min. prior to the administration of  $^{111}\text{In}$ -pentetreotide in a diagnostic amount of 220 MBq (patients 12, 13, 14, 15), or in a therapeutic amount of 7 GBq (patients 16, 17).

patient	maximum potassium (K) level
12	5.2
13	6.8
14	6.7
15	5.4
16	5.0
17	6.3

Patient no. 17 showed transient muscle weakness, the other patients had no symptoms related to the infusion.

### EXAMPLE 3

Effect of different amino acid preparations on [ $^{111}\text{In}$ -DTPA]octreotide uptake in the kidney

At least 5 patients received one of the following amino acid preparations:

1. AA (2030 mL cocktail of various amino acids; see MATERIALS, paragraph B, for the source and details)

2. 25 g L-lysine in 500 mL (see MATERIALS, paragraph C, for exact formulation)
3. 50 g lysine in 2000 mL (see MATERIALS, paragraph C, for exact formulation)
- 5 4. 75 g lysine in 1500 mL (see MATERIALS, paragraph C, for exact formulation)
5. 25 g L-lysine and 25 g L-arginine in 1000 mL (invention), (**Lys/Arg**; see MATERIALS, paragraph A. for exact formulation).

10       The preparations were given intravenously over 4 hours starting 30 minutes before treatment with the radioligand started. The radioligand was  $^{111}\text{In}$ -pentetreotide, either in a diagnostic amount of 220 MBq, or in a therapeutic amount, 7 - 11 GBq. Each patient was  
15 his or her own control. The control consisted of treatment with the radioligand but without an amino acid preparation.

At 24 and 48 hours post infusion the ratio between tissue uptake in the left kidney in patients  
20 receiving an amino acid composition and the controls was determined by planar scintigraphy and dosimetry.

Figure 4 gives the results of this study, which also includes the data obtained in patients described in examples 1 and 2. Although 75 g L-lysine leads to the  
25 highest uptake reduction, it was found that it resulted in severe hyperkalemia (Table 2). No hyperkalemia was found in the second best amino acid composition comprising 25 g L-lysine plus 25 g L-arginine (Table 1). Moreover, it was found that more patients vomited that  
30 received the AA compositions than patients receiving L-lysine or Lys/Arg (see also EXAMPLES 4, 5, 6).

#### EXAMPLE 4

35 Effect of prior art amino acid composition on vomiting

26 patients received 1 to 5 therapeutic doses of 1-10 GBq  $^{90}\text{Y}$ -DOTA, Tyr<sup>3</sup>-octreotide, with concomitant infusion of a 2030 mL cocktail of various amino acids in

4 hours, starting 30 min. before the administration of the radiopharmaceutical (see MATERIALS, paragraph B. for exact details). In 11 of these 26 patients (42%), [being 20 of 84 treatments (24%)] one or more episodes of vomiting occurred, up to 30 episodes of severe vomiting per treatment.

In one of these 11 patients the vomiting was so severe during the 2 treatments with the above described regimen, that it was decided to use an infusion with 50 g of L-lysine instead of the infusion with the cocktail of various amino acids concomitant with his 3rd and 4th therapy with  $^{90}\text{Y}$ -DOTA, Tyr<sup>3</sup>-octreotide. Only one episode of vomiting occurred after his 3rd treatment and no vomiting at all after his 4th treatment.

#### EXAMPLE 5

##### Effect of lysine on vomiting

8 patients received multiple therapeutic doses of 7-11 GBq  $^{111}\text{In}$ -pentetreotide. All received once a concomitant infusion of a 2030 mL cocktail of various amino acids in 4 hours, starting 30 min. before the administration of the radiopharmaceutical (see MATERIALS, paragraph B. for exact details). In 4 of these 8 patients (50%) vomiting occurred.

In these same 8 patients only 3 episodes (9%) of vomiting occurred during 22 treatments with 7-11 GBq  $^{111}\text{In}$ -pentetreotide while they received 25 or 50 grams of L-lysine in 500 to 2000 mL (see MATERIALS, paragraph C. for exact details) over 4 hours, starting 30 min. before administration of the radiopharmaceutical, as concomitant infusions.

In these same 8 patients only 3 episodes (6%) of vomiting occurred during 52 treatments while they received no concomitant infusion at all.



**EXAMPLE 6**Effect of **Lys/Arg** on vomiting

In an experiment of the invention 11 patients  
5 received an infusion over 4 hours of a solution  
containing 25 g L-lysine and 25 g L-arginine in 1000 mL  
(**Lys/Arg**; see MATERIALS, paragraph A. for exact  
formulation). Thirty min. after the start of the infusion  
they received a diagnostic dose of 220 MBq <sup>111</sup>In-  
10 pentetreotide. Ten patients had no symptoms during the  
infusion, in particular no vomiting. One patient had  
subfebrile temperature, malaise and nausea already before  
the start of the infusion, presumably caused by tumor  
necrosis. During the **Lys/Arg** infusion she vomited twice.  
15 This patient has tolerated the **Lys/Arg** infusion without  
any problems on all 4 later occasions, while receiving a  
therapeutic dose of 10-11 GBq <sup>111</sup>In-pentetreotide.

Five patients received the **Lys/Arg** infusion in  
the same manner as described above, but they received a  
20 therapeutic dose of 1850 MBq [<sup>177</sup>Lu-DOTA,Tyr<sup>3</sup>]octreotate,  
30 min. after the start of the **Lys/Arg** infusion. None of  
these 5 patients had any symptoms at all, in particular  
no vomiting.

Until now the **Lys/Arg** infusion, 1000 mL in 4  
25 hours concomitant with therapeutic doses of radioactive  
labelled peptides, has been administered to more than 30  
patients, in total more than 80 occasions. Vomiting  
occurs in less than 5% of the occasions, and if it occurs  
it is most probably due to other causes.

30  
From these studies described in EXAMPLES 4, 5  
and 6 it was concluded that the infusion of 2030 mL  
containing a cocktail of various amino acids causes  
frequent vomiting, which is unacceptable for routine  
35 clinical circumstances. On the other hand, vomiting is  
seldomly observed either with L-lysine infusions or with  
**Lys/Arg** infusion.